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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/049,847	03/27/1998	SYLVIE BAY	102.166A	6142

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/049,847	BAY ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-32,38-40,42-44 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-32,38-40,42-44 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

As a preliminary matter, in response to the Letter of 3/23/04, the instant application is not under RCE since a non-final Office action has been issued on 1/25/03.

Status of Claims

Claims 1-28, 33-37, 41 and 45-46 have been cancelled.

Claims 29-32, 35, 38-40, 42-44 and 47 are under consideration and examination.

Specification

The objection to the disclosure has been obviated with the correction to the sequence listing.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-32, 38-40, 42-44, 47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention for reasons advanced in the last Office action.

Response to Arguments

Applicant's arguments filed 7/23/03 have been fully considered but they are not persuasive.

A). Applicants point out that support can be found in the passage corresponding to the box portion of page 7 filed concurrently. It specifies that the claimed conjugate comprise at least 3 lysines and up to 15 lysine residues covalently linked to one another. Then, from the whole structure depicted in Figure 1, the only allowed variability exclusively concerns the central lysine residue. For the conjugates of Formula B4-T4-M (first one) and B2-T2-M the number of lysine residues is at least 3 and up to 15 when n is an integer from 1 to 13. Similarly, for the conjugates of Formula B8-T-8- M and B4-T 4-M (second one), the number of lysine residues is at least 3 and up to 15 when m is an integer from 1 to 9. Moreover, Example 1 discloses the complete protocol for the synthesis of a preferred embodiment of the claimed carbohydrate peptide conjugate. One skilled in the art starting from the exhaustive method of synthesis disclosed in Example 1 is fully capable of

adapting the protocol for synthesizing any of the claimed conjugates.

In response, there is nothing in the cited section of boxed page 7 that defines for a variable m or n and picking and choosing the variable numbers that can be encompassed by m and n. Nor does Figure 1 recites for the variables m and n. In fact, the K residues in Figure 1 are all defined and fixed. The test whether a term is supported in the as-filed specification is not whether one skilled in the art would be able to synthesize the claimed conjugates. Rather, whether the term is supported in the as-filed specification. The as-filed specification does not provide support for the m and n variables as broken down and assigned by applicants' arguments.

B. The response above applies herein since applicants present the same argument above in combination with Figure 1.

The rejection of the claims, as amended in the last Office is maintained for reasons set forth in the last Office action under paragraph A and reiterated below.

A. The specification fails to provide a written description for a vaccine or immunogenic composition effective against tumors using the conjugate. A vaccine indicates a protective effect against all or any kinds of tumors. The complex nature of tumors, let alone its cure, to date remains still elusive. For

some tumors, the etiologic agent that causes said tumor remains undefined. To date agents believed to have therapeutic effect against tumors are only candidates or promising leads for said therapy. Example (3) in the specification, page 27 describes protection induce by the conjugate against murine adenocarcinoma in mice. There is no indication whether similar results can be obtained for the claimed humans, or that the specific tumor, adenocarcinoma, using any of the conjugate or combinations would be applicable for all types of tumors to all humans. [Note applicants' statement at page 9 of the instant REMARKS relying on the Dalgleish reference as to the "numerous problems which are encountered when an anti-tumor immune response is desired"].

Also, the specification fails to provide an adequate description of the different derivatives of the carbohydrate tumor antigen. The specification provides a general description of the derivative. Other than the general description, the exemplification is nil or directed to the single sugar moiety galactosyl-N-acetyl serine. Even for this single sugar moiety, it does not describe the other different carbohydrates included in the scope of the claimed different forms of the B conjugate coupled to the dendrimer or method of said coupling.

Response to Arguments

Applicants traverse the Examiner's objection (sic, rejection) concerning the written description for a vaccine or an immunogenic composition. The experimental results shown in Examples 3 and 4 clearly demonstrate the usefulness of the claimed conjugates as the active ingredients of either an immunogenic composition or a vaccine composition. Example 4 clearly shows that a composition containing a carbohydrate peptide conjugate of the invention induce the production of antibodies which are recognized by a human adenocarcinoma. Such a composition clearly consists an immunogenic composition since it is able to raise the production of specific antibodies against a tumor.

In reply, an immunogenic composition is not the same as a vaccine. While immunogenic composition would raise antibodies however, it cannot provide the protective effect required of a vaccine. As applicants recognized at page 18 of the instant REMARKS "……one skilled in the art who had knowledge that raising antibodies against tumor antigens was a highly difficult test…"

It is further argued that Example 3 show that a composition containing a carbohydrate peptide conjugate of the invention induces the protection of adenocarcinoma-bearing mice. These results clearly demonstrate that a composition of the invention may also consist of an effective vaccine composition to protect

cancer-bearing animals. Moreover, the successful results obtained with an immunogenic composition or a vaccine composition of the invention is directly transposable to humans. A support for said transposition to cancer bearing human is illustrated by the enclosed article of Longenecker et al. Longenecker et al shows that an antigenic construct containing a synthetic carbohydrate antigen induces, both in mice and in humans, specific antibodies recognizing the synthetic tumor antigen as well as an anti-cancer protective immune response (see Table 5 on page 288).

In response, the claims do not recite for a specific tumor, as the argued adenocarcinoma. Rather only a vaccine or an immunogenic composition against any type of tumor. Longenecker discloses immunization against Tf carbohydrate epitopes containing tumor such as ovarian and breast cancers. There is nothing in Longenecker that extrapolates these to any type of tumors as claimed and argued.

Applicants concede that it is true that the rays of a protective anti-cancer immune response was highly unpredictable when using prior art antigenic constructs but once it is shown that a specific antigenic construct and specifically, the carbohydrate peptide conjugates of the present invention raise an anti-cancer protective response in animals specifically, in

mice, the efficiency of the implementation of these conjugates for treating humans is directly transposable. Applicants will concede the Examiner is perfectly correct when she underlines that the claimed carbohydrate peptide conjugates will not be effective for treating all types of tumors. Indeed, the claimed carbohydrate peptide conjugates will be efficient exclusively for inducing a protective immune response in patients suffering from cancers wherein the tumor express a carbohydrate moiety against which the immune response is sought. (Underlinings supplied).

With respect to the Examiner's objection (rejection) to the specification for failing to provide an adequate description of the different derivatives of the carbohydrate tumor antigen, Applicants respectfully disagree with the same. A derivative in the general understanding of one skilled in the art consists of a compound than can be imagined to arise from a parent compound by replacement of one atom with another atom or a group of atoms. This is used extensively in organic chemistry to assist in identifying compounds. The expression "derivative thereof" when this expression relates to a carbohydrate may, for example, be referred to in the definition included in the USPTO

Official classification, class 536, subclass 1.11, a copy of which is enclosed herewith. It is clear from the specification that every carbohydrate which consists of a natural tumor antigen and every carbohydrate moiety having chemical differences regarding the natural tumor antigen, but which may induce a protective immune response against the natural antigen can be used. It should be noted that the essential feature of the claimed carbohydrate peptide conjugates consist of the combination of 1) the specific structures of the dendrimeric polylysine residues or the lysine core, combined with 2) the presence of a B-cell epitope consisting of a carbohydrate moiety which, when associated with a T-cell epitope within the same antigenic construct, possess the property of inducing a protective anti-cancer immune response.

In response, it is not the definition of the term (derivative) that is at issue. As correctly pointed out by applicants, the term encompasses an enormous scope for which the specification does not teach a single derivative. Furthermore, it is not clear as to the essentiality of a derivative in the claim. As applicants state the essential feature lies in the combination of the structures of the polylysine in the presence of a B-cell epitope. It is little wonder that the specification does not enable even a single derivative. As indicated by

applicants because of the unpredictability in the tumor treatment, it is not apparent whether a derivative, i.e., a modified form of the carbohydrate would still exhibit the desired effect.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-32, 38-40, 42-44, 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. for reasons set forth in the last Office action.

In view of the amendments to some of the claims, cancellation of some claims and applicants' arguments, some of the rejections (not objection) have been overcome. The rejections of some claims that are maintained are rebutted below.

Response to Arguments

1. "B denotes a structurally defined carbohydrate moiety" is indefinite since there is no structure defined in the claims for the carbohydrate tumor antigen.

Since applicants have not responded to this rejection, it is believed that applicants are acquiescing therewith.

2. In claim 35" the carbohydrate is grafted" is unclear as to how grafting of said carbohydrate is achieved.

Applicants argue that page 17 of the specification, as enclosed, recites said grafting.

In response, this section recites synthesis method, not grafting. This is not the same. Applicants might be their own lexicographer carries with it the notation that applicants have to used terms that are consistent with the specification or prior art teachings.

4. Claim 40 is indefinite as to the other components comprised in the vaccine. This is a duplicate of claim 39 except that it functions as a vaccine. Likewise, claims 42-43 are duplicates of the composition. Recitation of the function of the composition does not make a composition different. "Capable" denotes uncertainty. "More" efficient (claim 43), "increasing" the survival are relative terms, the basis or standard by which said terms are measured are unclear, especially for all kinds of tumors.

Applicants argue that the essential feature of the claimed vaccine consists of the conjugate which is the active ingredient

to raise a protective anti-cancer immune response in the patient to which the vaccine is administered. The said vaccine beyond the carbohydrate peptide conjugate of the invention may also comprise an adjuvant of immunity or other conventional excipients which are to be included in normal vaccine compositions.

In reply, in the absence of the differentiating components, the composition is the same except for the functional limitation as a vaccine or immunogenic composition.

Double Patenting

Claims 29-32, 38-40, 42-44, 47 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-14, 24-29 and 33-36 of copending Application No. 09/405,986(the '986 application) for reasons of record.

Response to Arguments

In view of the terminal disclaimer of record, this rejection no longer stands.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29-32, 38-40, 42-44, 47 are rejected under 35 U.S.C. 103(a) as being obvious over Chong et al (5,679,352) for reasons stated in the previous Office actions or Chong in combination with Jondal (5,807,559).

Response to Arguments

Applicants argue that Chong et al exclusively discloses dendrimeric conjugates which combine only peptide T and B-epitopes. Chong et al does not disclose or suggest any synthetic conjugate wherein the B-epitope is included in a carbohydrate moiety. In lines 39 to 48 of col. 2, it is argued that the technical solution found by Chong et al to induce an immune response consists of using synthetic peptides containing immune-dominant epitopes from Hi OMPS as additional antigens. The synthetic carbohydrate PRP oligomers that may be present in

the conjugate disclosed by Chong et al are exclusively used as T-cell epitopes as can be seen from lines 32 to 37 of column 3.

In reply, whether the synthetic carbohydrate used by Chong functions as T-cell epitopes, is immaterial, as the compound conjugate is a known conjugate. It will be within the ordinary skill in the art to determine the function of the components in the conjugate, if not inherent to the prior art disclosure. A B-cell response normally requires or accompanies a T-cell response.

In considering disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also inferences which one skilled in the art would reasonably be expected to draw therefrom. In re Preda, 159 USPQ 342; In re DeLise 160 USPQ 806. Absolute predictability is not a prerequisite of obviousness.

Applicants argue that the synthetic conjugate disclosed contains exclusively peptide B and T-epitopes and that the PRP carbohydrate moiety is used as a carrier for these epitopes.

In reply, as stated above whether the carbohydrate moiety is used as a carrier is immaterial to the known conjugate. It is well known in the art that carrier elicits also immune responses.

Attention is drawn to Chong at col. 17, lines 27-32 which discloses that the synthetic glycoconjugate may be used to produce vaccines eliciting antibodies against proteins or

oligosaccharide. Such vaccines may be used to induce immunity toward tumor cells, or to produce antitumor antibodies. It is noteworthy to cite applicants' recognition in the REMARKS of 5/3/01 that Chong et al at lines 38-43, col. 3, is concerned with the enhancement of carbohydrate immunogenicity by the use of MAP type constructions containing Hib determinant as carrier molecules for the carbohydrate moiety, more precisely, the PRP carbohydrate moiety. Applicants further recognized, col. 5, lines 29-39 that Chong encompasses the use of peptides consisting of immunodominant epitope for T-cells as PRP carriers or as autologous or heterologous B-cell epitope carriers.

Applicants again incorporate the prior remarks concerning the Schreiber, the Pardoll and the Dalgleish references cited in the prior responses. These references are argued as never been commented on by the Examiner.

In response, applicants' attention is directed to the last Office action. It stated that "the three references rely upon does not disclose any conjugate and nothing more than a general teaching of a tumor vaccine."

Applicants admit that Jondal discloses an antigenic construct consisting of a carrier molecule, namely, KLH which is fused to an antigenic moiety consisting of a peptide bearing T-cell epitope capable of binding a MHC Class 1 molecule and a carbohydrate component having the same immunogenic characteristics of the carbohydrate structure on the tumor cell

infectious agent or the infected cells as can be seen from the Abstract. But argue that the antigenic constructs are aimed to induce a cytotoxic T-cell response against the carbohydrate structures and never an antibody response.

In response, applicants' arguments are not commensurate in scope with example, claim 29 which does not require a response of the conjugate. The disclosure of Jondal, col. 10, Table 1 supports the findings of Chong. Jondal discloses a conjugate of protein and tumor or bacterial antigen effective as anti-tumor or anti-bacterial antigen i.e., depending upon the vaccine or immunity one desires i.e., whether an antitumor or antibacterial vaccine. The important aspect of the conjugation of protein-polysaccharide conjugates is the desire to elicit both T and B cells responses.

Accordingly, the teachings of Chong, alone or in combination with Jondal render the claimed invention prima facie obvious.

No claims are allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action

is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (703) 308-3967. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
July 10, 2004